## **REMARKS**

### **Preliminary Remarks**

Applicants' Request for Continued Examination filed July 30, 2004 has been granted by the Examiner.

Claims 2-3, 5-6, 12, 16, 18-19, 22-23, 27, 32-33, 36-37, and 44-45 have been previously canceled. Claim 41 has been canceled without prejudice herein. Claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-40, 42-43 and 46-50 will be pending in this application upon entry of this amendment.

Independent claims 1, 15, 30, and 42 are amended to specify a method for inducing T cell non-responsiveness to a donor antigen, or to a donor cell, tissue or organ that expresses at least one such antigen, by administering the tolerizing agents of the invention from five to eight days prior to transplantation of the tissue or organ to be transplanted. Support for a five to eight day prior administration period can be found in the specification, for example, on page 11, lines 6-7, and page 14, lines 30-33.

Claims 15 and 42 have been further reworded to improve the readability of the claim, without affecting the substance of the claimed matter. Support for induction of T cell non-responsiveness in the recipient to the allogeneic or xenogeneic tissue or organ can be found in the specification, for example, at page 9, lines 31-34. Support for a donor cell can be found in the specification, for example, at page 5, lines 4-9.

No new matter has been introduced by these amendments. Therefore, entry and consideration of the amendments are respectfully requested.

#### 35 U.S.C. § 103(a) (Obviousness)

Claims 1, 4, 5, 7-15, 17, 18, 20-32, 34-44, and 46-50 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. ("Lederman") in view of U.S. Patent No. 5,597,563 to Beschorner et al. ("Beshorner") and U.S. Patent No. 6,056,956 to

Cobbold et al. ("Cobbold") (collectively the "tolerization references"), for the reasons stated in the Office Action.

Applicants respectfully traverse this rejection, for the reason that no combination of the cited references would have given the skilled artisan any incentive to induce T cell non-responsiveness to an allogeneic or xenogeneic donor tissue or organ in a human recipient comprising administering (a) a donor cell and (b) an anti-human gp39 antibody, or human soluble CD40 molecule, much less any reasonable expectation of success in doing so.

However, to advance prosecution, while in no way agreeing with the Examiner's contentions that the claims of the instant invention are rendered obvious by the tolerization references, Applicants have amended the claims to specify a method for inducing T cell non-responsiveness to a donor antigen, or to a donor cell, tissue or organ that expresses at least one such antigen, by administering the tolerizing agents of the invention from five to eight days prior to transplantation of the tissue or organ to be transplanted. Administration of tolerizing agents within a five to eight day period prior to transplantation is not taught or suggested by any combination of the above-cited references.

Lederman describes antibodies to an uncharacterized antigen (5c8) present on activated but not resting T-cells, which antibody inhibited T-cell activation of B-cells. Lederman does not teach or suggest any method for administration of tolerizing agents prior to transplantation; therefore, Lederman does not make obvious the methods of the invention as claimed.

Beschorner teaches induction of antigen-specific tolerance by administration of Antigen Presenting Cells (APCs). Beschorner suggests administering an immunosuppressive agent—specifically, an immunosuppressive agent such as Cyclosporin A "which depletes the thymic medulla of APCs" continuously from "2 to about 20 days, preferably about 14 days" (column 8, first paragraph). In this passage Beschorner specifies use of an immunosuppressant for depletion of APCs, *not* the use of a T-cell immunosuppressant, *nor* does Beschorner teach anything resembling how many days this treatment should be administered prior to transplantation. Beschorner then indicates that an immunosuppressive agent can be administered "from about 1 day to about 90 days before infusion of the tolerogenic APCs until about 7 days to about 90 days after the infusion of

tolerogenic APCs" with a preferred range of "about 7 days to about 28 days before infusion of the tolerogenic APCs until about 7 days to about 28 days after the infusion of tolerogenic APCs" (column 8, line 65 to column 9, line 5). Further, Beschorner teaches that the immunosuppressive agent should be administered for a period of time long enough to deplete the thymic medulla of APCs (column 5, lines 13-15). Given the broad time frames in these teachings, Beschorner in effect teaches away from administration of gp39 antibody in a narrow 5 to 8 day period. Further, Beschorner does not teach administration of an immunosuppressive agent resembling gp39, nor does Beschorner teach administration of tolerizing agents in any time frame relative to when the actual donor organ or tissue is transplanted. Therefore, Beschorner does not teach the methods of the instant invention as claimed.

Cobbold teaches tolerance to an antigen by administration of CD4 and CD8 antibodies. Cobbold suggests administration of the antigen "from up to 5 days before" administration of antibodies to "up to 5 days or even 2 to 3 weeks after the course [of antibody treatment] has been completed" (column 3, lines 39-43). Cobbold, like Beschorner, does not teach any time frame for administration of tolerizing antibodies and/or antigen *relative to time of transplant*. Therefore, Cobbold does not teach the methods of the instant invention as claimed.

Under no combination of Lederman, Beschorner, or Cobbold may be found teaching, suggestion, or motivation to administer gp39 antibody and donor cells from 5 to 8 days prior to the transplantation of allogeneic or xenogeneic donor tissues or organs. Therefore, the combination of these references fails to make obvious the claimed methods of the invention.

The Examiner further asserted that there does not appear to be a manipulative difference in the method steps of the instant invention and the cited references. Applicants submit that the concrete time frame for administration of the tolerizing agents of the invention as now claimed represents a significant difference in the method of tolerizing transplant recipients, a time frame which is in no way provided in the cited references. Prior to the disclosure of the instant invention, one of skill in the art attempting to tolerize an individual using an immunosuppressive agent would lack guidance as to the critical time frame and sequence for applying donor cells and gp39 antibodies as an immunosuppressive agent, relative to transplantation of the donor tissue, in order to

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achieve success. Using the methods of the invention as claimed, such a skilled artisan now has the tools in hand to properly tolerize a patient in need of an organ transplant using the gp39 antibodies of the invention.

For the reasons discussed above, the applicants submit that the present claims satisfy the requirements of 35 U.S.C. § 103(a), and request that the rejection of claims under § 103(a) be withdrawn.

# Judicially created doctrine of obviousness-type double patenting

Claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-40, 42-43 and 46-50 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

claims 1-34 of U.S. Patent No. 5,683,693, claims 1-34 of U.S. Patent No. 5,902,585, and claims 1-7 of U.S. Patent No. 6,375,950.

Applicants submit that the claims as amended in the present response are patentably distinct over the claims of the above-identified patents. The claims identified above do not claim a method for inducing T cell non-responsiveness to a donor antigen, or to a donor cell, tissue or organ that expresses at least one such antigen, by administering the tolerizing agents of the invention from five to eight days prior to transplantation of the tissue or organ to be transplanted. Administration of tolerizing agents within a five to eight day period prior to transplantation is not claimed in the above patents and is not obvious in view of these claims and the prior art. There is no teaching or suggestion of the five to eight day time period. Therefore, Applicants request that the rejection of the claims of the instant invention under the judicially created doctrine of obviousness-type double patenting be withdrawn.

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## **CONCLUSION**

Applicants respectfully request entry of the foregoing amendments and remarks in the prosecution of this application. If any points remain in issue, which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Dated: March 2, 2005

Respectfully submitted,

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